REMARKS

Claims 10 and 12–17 are pending in this application. The Examiner has withdrawn from consideration non-elected claims 16 and 17. By this Amendment, claims 10, 16, and 17 are amended and claim 11 is canceled. Support for the amendments to the claims may be found, for example, in the original claims and in the specification at page 19, lines 19–23. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Personal Interview

The courtesies extended to Applicants' representative by Examiners Salmon and Bausch at the interview held April 21, 2009, are appreciated. The reasons presented at the interview as warranting favorable action are incorporated into the remarks below, which constitute Applicants' record of the interview.

II. Enablement Rejection under 35 U.S.C. §112, First Paragraph

The Office Action rejects claims 10–15 under the enablement requirement of 35 U.S.C. §112, first paragraph. Specifically, the Office Action asserts that the specification does not provide predictable guidance for correlating any expression levels of SEQ ID NOs: 2, 3, 7, 8, 10, 22, 25, 29, and 34 to any prognosis of neuroblastoma. *See, e.g.*, Office Action at page 4. By this Amendment, claim 11 is canceled rendering its rejection moot. As to the remaining claims, Applicants respectfully traverse the rejection.

A. Scope of "Good Prognosis" and "Bad Prognosis"

The Office Action, on page 5, asserts that the claims are "drawn to detection of any type of good or poor prognosis" (emphasis added). The Office Action asserts that "any prognosis" would encompass "a determination of specific stages of tumor" and "prognosis of death, treatment, or recovery." *Id.*

In response, Applicants respectfully point out that claim 1 is directed to a "method for determining a good or poor prognosis" and does not recite "detection of good or poor prognosis" as asserted by the Office Action. The American Heritage College dictionary, 4th edition, defines "prognosis" as "a prediction of the probable course and outcome of a disease;" "the likelihood of recovery from a disease;" or "a forecast or prediction." As such, it would appear that a prognosis is something that is determined rather than detected.

Applicants respectfully disagree that "treatment" is a prognosis. Instead, treatment is a course of action decided upon based on a diagnosis and/or prognosis. Applicants also disagree that "a determination of specific stages of tumor" is a prognosis. The stage of a tumor is a clinical characterization of the tumor itself, not a forecast or prediction of the probable course and outcome of the disease.

Applicants respectfully disagree that "a good or poor prognosis" as recited in claim 10 presents a scope of enablement problem. As discussed above, a prognosis is a prediction--it is not a guarantee. Although there may be many possible prognoses with varying degrees of specificity (e.g. patient will die within 1 year, or patient has 14 days, 16 hours, 32 minutes, and 51 seconds to live), all that claim 10 requires with regard to the prognosis is that it is placed in one of two categories that are defined as "good" and "poor."

The specification clearly defines the distinguishing characteristics between a good prognosis and a poor prognosis so as to enable one of skill in the art to categorize a prognosis as "good" or "poor" based on the data obtained from the claimed methods First, the specification describes that 23 neuroblastoma patients were clinically characterized as having either a good prognosis or poor prognosis based on the stage of their tumor at the time of diagnosis and whether they died within 75 months of said diagnosis. *See* specification, page 23, lines 11–28. Those who had a stage 4 neuroblastoma or those that died within the 75-month follow-up period (regardless of the stage of the neuroblastoma) were classified as poor

prognosis patients, while the rest were classified as good prognosis patients (stage 1, 2, and 4s neuroblastoma patients who did not die during the 75-month follow-up period.) *Id.* at lines 23–28.

The specification then describes microarray analysis of samples from the 23 neuroblastoma patients. *See* specification, pages 25–27. The microarray analyzed the expression of approximately 10,000 different genes. *Id.* Out of these 10,000 genes, 37 genes were identified that clearly distinguish between the good prognosis patients and the poor prognosis patients. *Id.* Table 2 provides a list of these 37 genes and how they are differentially expressed in poor prognosis patients as compared to good prognosis patients.

The specification further indicates that these result were validated using expression data from RT-PCR. *See* specification, page 28, lines 1–4. To further test the validity of the discriminatory capacity of the expression profile of these 37 genes, 6 additional tumor samples from "test" patients without prior knowledge of their prognoses were tested and analyzed with respect to their expression profiles for the 37 genes, and were classified as good prognosis or poor prognosis after comparing the "test" expression profiles to the expression profiles previously obtained from the 23 clinically classified neuroblastoma patients. *See* specification, page 32, lines 13–22. All 6 tests were later verified as being correctly classified. *Id.*

The specification further describes a smaller panel of 9 genes out of the 37 genes that may be used "to discriminate very effectively between patients having a good prognosis and patients having a poor prognosis." *See* specification, page 37. The 6 "test" samples were also evaluated against this panel of genes, with all 6 tests later verified as being correctly classified. *Id.*

During the interview, the Examiners inquired as to how one of skill in the art, after obtaining the patient's expression levels for the 9 target genes, determines whether the patient

has good or poor prognosis. To clarify this, claim 10 is amended to recite in part, "performing cluster analysis of the expression profile of the patient with expression profiles of the target genes from patients previously clinically classified as good prognosis and expression profiles of the target genes from patients previously clinically classified as poor prognosis." Support for this amendment to claim 10 may be found, for example, in the specification at page 22, lines 1–20; page 26, lines 22–27; and page 32, lines 7–22.

Applicants respectfully submit that the use of bioinformatics, and specifically cluster analysis, for prognosis classification of cancer patients was well-known in the art, and involved routine procedures, at the time this application was filed, as evidenced by Mora, Takita, and both Ohira references.

B. Expression Levels

The Office Action, on page 9, asserts that Takita teaches "that both early and advanced stage [neuroblastoma] tumors are heterogeneous in expression." The Office Action asserts that Takita therefore teaches that tumor tissue in the same stage can have different expression profiles. *Id.* From these alleged teachings, the Office Action concludes that "it is unpredictable to correlated [sic] prognosis of any tumor sample because it is unpredictable [of] the expression levels in Stage 3 tumors. It is not clear if Stage 3 tumors have the same correlated expression as Stage 4 tumors." *See* Office Action, page 5.

In response, Applicants respectfully submit that the teachings of Takita are taken out of context and that the reference is not being considered as a whole. For example, the abstract of Takita indicates that the heterogeneous expression levels were observed from a two-way clustering analysis based on the expression pattern of approximately 500 genes selected from the expression data for approximately 1,700 genes. In the "Results" section, Takita provides more detail. Takita explains that out of the original 1,700 genes used to collect expression data, cluster analysis was performed on the 496 expressed genes that

passed pre-filtering. *See* page 123, 2nd column. Takita explains that out of these 496 genes, the top 30 genes showing a higher expression in the early-stage tumors (see Table 3), and the top 30 genes showing a higher expression in advanced-stage tumors (see Table 4) were selected to differentiate between early-stage and advanced-stage tumors. *See* page 124. Thus, despite the heterogeneous expression of the 1,700 genes, Takita was able to identify 60 genes that could be used to differentiate between early-stage and advanced-stage tumors.

C. Schramm et al.

The Office Action asserts that it is unpredictable that the gene expression associations observed in the instant specification are reproducible because Schramm et al. asserts a group of genes that is predictive of prognosis but does not overlap the genes asserted by the instant specification. In response, Applicants respectfully point out that Schramm et al. indicates that "several genome-wide mRNA expression profiling studies have identified reliable outcome predictors for neuroblastoma, but with little or no overlap in the decision-making genes" (emphasis added). *See* page 1, 1st column, 3rd sentence. Schramm et al. also teaches that "validation by real-time PCR, which is currently the gold standard for measuring gene expression, is considered to be the final proof of array data." As discussed above, the instant specification indicates that the microarray results were validated using expression data from RT-PCR. *See* specification, page 28, lines 1–4.

D. Conclusion

For at least the reasons presented above, Applicants respectfully submit that claims 10 and 12–15 are fully enabled by the specification coupled with knowledge that was available in the art at the time of filing. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 10–15 under 35 U.S.C. §102(b) over Mora et al., Cancer Letters, July 2003, vol. 197, p. 119 ("Mora") as evidenced by Affymetrix Human Genome U95 array as described in Affymetrix Product Catalog January 2001 ("Affymetrix"). By this Amendments, claim 11 is canceled rendering its rejection moot. As to the remaining claims, Applicants respectfully traverse the rejection.

First, as a preliminary matter, Applicants respectfully but adamantly disagree with the assertions made by the Office Action in paragraph 12 found on page 14. Specifically, the assertion that the Applicants' disclosure does not appear to add anything further to the teachings of Mora is completely unfounded and unsubstantiated and, thus, amounts to nothing more than a conclusory statement. Furthermore, the assertion is factually in error. Mora discloses carrying out microarray analysis using features for 63,175 genes/ESTs. *See* page 123, 1st column. Mora further discloses that unsupervised analysis of the gene expressions for all the samples revealed that tumor and cell lines had distinct expression profiles. *Id.* Mora suggests that specific genes that could help in discrimination between low-risk and high-risk tumors "could be identified." *See* page 123, paragraph bridging 1st and 2nd columns. However, Mora fails to disclose any procedures or analytical tools that could be used in identifying specific genes whose expression profiles could be successfully used to differentiate between low-risk and high-risk tumors, let alone identify nine specific genes whose expression profiles can be used to classify neuroblastoma patients as having a good prognosis or poor prognosis as defined and set forth in the instant specification.

Therefore, for at least these reasons, Applicants disclosure is not commensurate with the teachings of Mora as it adds much more guidance as to:

- procedures and validation of those procedures,
- multiple tools for statistical analysis of the expression data,

- positive identification of 37 genes whose expression profiles differentiate between good prognosis and poor prognosis patients, and

- disclosure of the under expression or over expression of good prognosis versus poor prognosis for each of the 37 genes to enable one of skill in the art to compare an expression profile based on said 37 genes of a patient against the under expression or over expression data and classify the patient as good prognosis or poor prognosis.

Third, as discussed above, "good prognosis" and "poor prognosis" have well-defined criteria that are clearly set forth in the specification (i.e., poor prognosis = differential expression profiles from patients who died within 75 months of diagnosis or who had stage 4 neuroblastoma; good prognosis = differential expression profiles from patients that did not die within 75 months of diagnosis and had stage 1, 2, or 4s neuroblastoma). Mora, on the other hand, discloses two prognostic groups -- "low-risk" and "high-risk" -- wherein the low-risk criteria were all the "non-stage 4 tumors that did not require cytotoxic therapy" and the high-risk criteria were all the "stage 4 tumors and those that eventually required cytotoxic therapy." *See* page 123, 1st column. Therefore, the prognostic criteria disclosed by Mora are different than those set forth in the Applicants' specification as Mora does not use death as a prognostic criteria and the prognostic criteria defined in the Applicants' specification does not include cytotoxic therapy.

Therefore, because Mora's two prognostic groups are defined by criteria that are different from those that define the good and poor prognostic groups recited in claim 10, Mora does not teach each and every limitation of claim 10 and, thus, does not anticipate the claim. Furthermore, Mora does not disclose the nine genes specifically recited in claim 10 nor does Mora expressly or inherently disclose how the expression profiles of those nine genes can be used to differentiate between a poor prognosis and a good prognosis.

Additionally, as discussed above, Mora cannot in any way be fairly or reasonably considered to provide an enabling disclosure such that it anticipates the claims.

For at least these reasons, Mora does not anticipate claim 10. Claims 12–15 variously depend from claim 10 and, thus, also are not anticipated by Mora. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

IV. Rejoinder

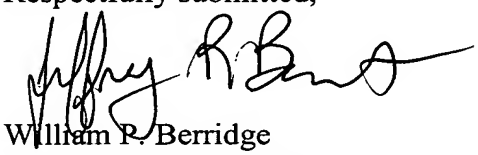
Applicants respectfully request rejoinder of claims 16 and 17. Claims 16 and 17, although requiring a larger combination of target genes than the elected combination of target genes, require in their combinations the elected combination as a subset. Therefore, if claim 10 is found allowable, then claims 16 and 17 should also be found allowable, as they require all the limitations of claim 10.

V. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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Date: April 27, 2009

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